CHAPTER 10

General discussion and future perspectives

In the early 19-th century, René Laënnec is believed to be the first physician who discovered, described and diagnosed bronchiectasis by using a now classical medical instrument that he called the stethoscope [1]. He was able to link his clinical assessment – as evidenced by the presence of abnormal chest sounds - to histopathological abnormalities of airways during autopsy and vividly described the nature of bronchiectasis, consisting of pathological dilatations with retention of purulent secretions [2].

In the two centuries that since have elapsed, bronchiectasis as a result of previous chest infection has become less common owing to the drop in tuberculosis in affluent parts of the world and due to improved hygiene and vaccination programs. Today, with chest infections still among the leading causes of bronchiectasis, immunodeficiencies and genetic disorders such as primary ciliary dyskinesia, Young's syndrome, and alpha-1-antitrypsin deficiency have been emerging as equally important underlying causes [3]. Although the morbidity and prognosis of bronchiectasis have improved, the incidence and prevalence is found to increase during the last two decades, especially in older age groups [4]. As a result still many patients suffer from this often debilitating condition that is accompanied by stigma and limited participation in social activities and that clearly impairs quality of life [5]. Not only do affected patients abstain from visiting theatres, cinemas or other social activities for fear of being frowned upon for their constant cough, but their ailment also generates high annual costs, arising from maintenance treatment, hospital admissions and days off work or school. In addition, recent work has confirmed noteworthy mortality rates [6]

Evidence based treatment modalities for bronchiectasis are sparse, and only macrolide maintenance treatment has been studied in more than one randomised clinical trial, among which the BAT trial in this thesis.

For decades, long-term macrolide treatments have been reserved for patients with relatively uncommon conditions such as cystic fibrosis and diffuse panbronchiolitis and perhaps the odd bronchiectasis patient with unusually severe symptoms. The higher awareness of bronchiectasis combined with the publication of trials which confirm the effectiveness and acceptable safety profile of long-term macrolide treatment, not just in bronchiectasis but also in patients with obstructive lung disease will expectedly result in a rapidly growing number of prescriptions for macrolide maintenance treatment [7;8]. This may be cause for concern for multiple reasons, which include cardiovascular side effects and above all the induction of macrolide resistance. Thus, since we have opened Pandora's box of apparently unrestricted possibilities for the long-term use of macrolides, the challenge we are facing now will be to keep that box no more than just ajar. For a restrictive and balanced use of macrolide treatment of bronchiectasis, a better phenotyping of bronchiectasis patients and a consensus-based definition of (a) predictor(s) of macrolide response would greatly help to advance the field.

Bronchiectasis is a disease with heterogeneous aetiology; many possible underlying causes have been described, ranging from frequently encountered conditions, such as asthma or pneumonia to rare immune- or genetic disorders. In addition, the clinical presentation and symptoms may be very different between different patients. A pseudomonas-colonised bronchiectasis patient with generalized saccular bronchiectasis, abundant sputum expectoration and frequent exacerbations may be considered a different disease phenotype and requires a different type of treatment than the patient with sparse, cylindrical bronchiectasis as a result of traction from fibrosis caused by systemic disease, with only limited sputum production occasionally growing *Haemophilus influenzae*, and without apparent exacerbations.

The introduction of a targeted treatment approach necessitates careful phenotyping of bronchiectasis patients [9]. Expectedly, better understanding of the different categories of bronchiectasis patients will also help to predict which patient group benefits the most from a certain treatment modality, and as such attribute to a judicious application of macrolide treatment. Therefore, it is important to gain more insight into which specific traits set the one bronchiectasis patient apart from the other. And in addition to define in which patient the benefits of a certain treatment are expected to outweigh the possible downsides. Once that has been made clear, the next step should be the application of tailored treatment for each of the patient groups. Looking at the studies in this thesis, a good response to macrolide treatment might be predicted by inflammatory markers, radiological characteristics or clinical correlates of disease, such as exacerbation frequency, all of which will now be discussed in further detail.

The current guidelines use the frequency of infectious exacerbations to direct the application of macrolide maintenance treatment, restricting this treatment to patients with three or more yearly exacerbations [10]. Of note, two out of three trials showing benefit of macrolide maintenance also included patients with a lower number of exacerbations (< 1 or 2 exacerbations yearly). However, the number of exacerbations in patients that were eventually included in those trials was generally much higher than suggested by the inclusion criteria (mean number of 3.6 in EMBRACE (inclusion criterion 1 or more), and 30% of patients with >5 exacerbations in BLESS (inclusion criterion 2 or more). In addition, the net reduction of exacerbations was largest in the BAT trial, which included patients with the highest number of exacerbations (mean 4.5/year). In an exploratory subgroup analysis of data from the BLESS trial the authors demonstrated the largest reduction in exacerbations in patients with 5 or more exacerbations yearly. This may suggest a tendency to macrolide response in patients with frequent exacerbations. Discerning and selecting patients for a given treatment modality by the frequency of their infectious exacerbations has the evident advantage of being a simple and widely applicable way to categorize patients without need for additional testing, which may therefore also be of use in low income countries with their

relatively high prevalence of the disease. Currently, our group is trying to shed a light on this subject by merging results from BAT, BLESS and EMBRACE trials. We hypothesise that it will be possible to define a 'frequent exacerbator' subtype with a distinct response to macrolide treatment.

Another way to characterize bronchiectasis patients would be by the type and extent of the inflammatory response(s). The 'vicious circle' hypothesis, already in the 19-eighties proposed by P.T. Cole and still generally accepted, states that airway inflammation plays a central role in bronchiectasis [11]. Macrolides are considered to have an anti-inflammatory effect and have been proven effective in bronchiectasis, however, many questions about the exact mechanism of action are still unanswered. The identification of a marker of macrolide responsiveness may not only help to gain insight in the macrolide mechanism of action but could also be of use in selecting those patients who are expected to benefit the most from this treatment modality. Blood biomarkers, such as CRP, are increasingly recognized as markers of inflammation in other diseases, but were found not to reliably reflect the extent of the inflammatory response in the airways of CF patients [12]. Our longitudinal data on CRP-levels and white blood cell count during macrolide treatment extends this finding to the bronchiectasis patients; CRP levels and WBC were overall low and not significantly different between responders (n=34) and non-responders (n=7) to treatment and may therefore not be the most promising markers.

In contrast to blood biomarkers, inflammatory markers in sputum of bronchiectasis patients were found to give a good impression of the augmented inflammatory process underlying bronchiectasis. Even in a clinically stable situation, increased levels of neutrophils and neutrophilic chemo-attractants, the most important of which are believed to be IL-8, IL-1β, IL-17, TNF-α and LTB-4 are present in the airways of patients with bronchiectasis [13;14]. Small studies have shown that markers of neutrophilic inflammation are among those that are primarily suppressed during macrolide treatment [15;16]. The quantity of the neutrophilic inflammatory response, as measured by the presence of sputum neutrophilia, neutrophil chemo attractants, neutrophilic degranulation products, or a combination, might be therefore be predictive of a favourable response to macrolide maintenance treatment. Sputum neutrophil counts are among the more readily available measurements in most clinics and may therefore be the most interesting measure for use in clinical practice, but more extensive testing for inflammatory markers may be primarily restricted to research settings as interesting endpoints for future trials on macrolide treatment. In order to facilitate widespread clinical use of sputum markers, a first requirement is the possibility to use spontaneously expectorated sputum. In CF, both spontaneously expectorated and induced sputum have been used to measure and type the inflammatory response [12]. In addition, recent work showed high levels of inflammatory markers in spontaneous sputum, which is confirmed by our own analysis of sputum samples which shows markedly elevated

levels of IL-1 β, IL-8, IL-10, MPO and TNF-α, among other inflammatory markers (Altenburg et al, non-published data) [9;17], suggesting that spontaneous sputum may be a reliable way to investigate lower airway inflammation.

Another indicator of disease severity that is readily available in clinical practice is the extent of radiological abnormalities as seen on chest CT scans and certain features may also predict macrolide responsiveness. In chapter 5 we state that CT abnormalities indicative for active inflammation, such as mucus plugging and bronchial wall thickness have been noted to improve during macrolide treatment. In addition, in an exploratory analysis of the BAT trial results we discriminated responders and non-responders based on differences in bronchial wall thickness (mucus plugging was not accounted for in our study). Since CT scanning is the gold standard for the diagnosis of bronchiectasis and will therefore be available for almost each patient with this diagnosis, CT-based guidance for the allocation of macrolide treatment would be very attractive. Future studies in this direction should focus on the above mentioned features indicative of active inflammation, ensure adequate CT-quality as to facilitate the use of validated scoring systems and use CT severity as a secondary or even primary endpoint in clinical trials of maintenance treatment. Low dose CT scans, with radiation doses similar to those used in conventional chest radiography are commonly used for the follow up of pulmonary nodules. Recently, authors have stated that dose-reduced CT scans may also be used for diagnosing and monitoring bronchiectasis [18;19]. Considering a possible rise in the number of CT-scans for clinical- and research purposes, this is a very interesting development and deserves to be further explored.

In our exploratory study of the dose-effect relationship in azithromycin maintenance treatment, we found stable concentrations of azithromycin in sputum, as opposed to variable serum levels, but these findings need to be confirmed in studies primarily designed for PK/PD purposes. Other findings, such as a relation between azithromycin sputum levels and suppression of systemic inflammation are only theoretically explained yet.

These and other gaps in our knowledge on the pharmacokinetic characteristics of long-term macrolide treatment have led to a lack of uniformity with concern to macrolide dosing regimens worldwide, which are usually copied from the field of CF and blended with local habits and traditions. In addition, there is no evidence-based information on the ideal duration of treatment as we are unaware whether, and if so, when, azithromycin's beneficial effect – or benefit/harm ratio may decrease over time.

One might get an idea on the sustainability of the treatment effect from the three randomized trials on macrolide treatment, since both BAT and BLESS trials demonstrated a sustained effect of macrolide treatment on clinical outcome parameters such as lung function and quality of life during one year of macrolide treatment. The effect subsided in the 2-4 month

run-out period of the BAT trial when treatment was discontinued as did the advantages of 6 months of macrolide treatment in the EMBRACE trial in the following 6 months of follow up. [20-22].

There is an urgent need for additional evidence in this specific area in order to further optimize the azithromycin dosing regimen and treatment duration. For a start this could be done as simple as performing a careful longitudinal cohort-follow up of the many bronchiectasis patients who are currently started on azithromycin maintenance treatment. Long-term follow up of well-defined patient groups on macrolide treatment e.g., former randomized trial participants, would provide interesting information about both the sustainability of the benefits and about the evolution of potentially deleterious effects during extended periods of macrolide treatment. Since the 'antibiotic holiday' (abstaining from macrolide treatment during the summer months) has become common practice, appreciated by both physicians and patients, ample opportunity exists for further study into this interesting and maybe promising habit.

In addition, measuring concentrations of azithromycin in serum, sputum and perhaps also lung tissue samples (if available) would provide important information about the long-term PK and PD of azithromycin during 'steady state'.

We believe that it is likely that gaining evidence on duration, dosing and frequency of azithromycin maintenance treatment will result in a more careful and tailored prescription behaviour. This is particularly important in view of induction of macrolide resistance, a major potential disadvantage of this treatment modality, but will also help in minimizing other adverse effects.

Long-term use of antibiotics is associated with the induction of microbial resistance against the agent(s) concerned. This is particularly true for azithromycin that has been shown to cause a more substantial and sustained increase in macrolide resistance among respiratory tract pathogens as compared to other macrolide antibiotics, possibly because of its long half-life [23;24]. In addition, a significant association between macrolide prescribing and resistance has been demonstrated [24-26].

Randomized trials of long-term macrolide treatment consistently report an increase in both the proportions of macrolide resistant oropharyngeal streptococci and macrolide resistance in sputum pathogens in participating patients, with macrolide resistance rates of sputum pathogens up to 90% [20-22;27]. In addition, molecular analyses of respiratory samples (16S rRNA sequencing) during erythromycin treatment for bronchiectasis showed substantial change to the airway microbiota, more specifically an increase in intrinsically macrolide-tolerant organisms [28].

But, is this emergence of resistance cause for actual concern? We believe the answer to this question is 'yes, but it depends on who and what we are looking at'. In the individual macrolide-treated patient, no additional mortality or treatment failure has been shown from infections caused by macrolide-resistant pathogens [29;30]. Moreover, macrolide maintenance treatment even caused a substantial reduction of the total number of sputum pathogens and significantly higher eradication rates [20-22;31]. But, although deleterious effects of long-term use of antibiotics on both the nasopharyngeal and faecal microbiota have been described for the individual patient, the real danger of resistance induction lies in the increase of macrolide resistance on a population level [32].

Macrolide resistant pathogens in asymptomatic (and therefore untreated) carriers may be transferred to vulnerable hosts. As such, increasing number of difficult-to-treat infections caused by macrolide resistant pathogens in children and immune-compromised patients have been reported, and additionally, transfer of resistance determinants from commensals to pathogens is likely to occur [33-35].

Most trials on macrolide maintenance treatment in bronchiectasis have focussed on development of resistance in pathogens cultured from sputum samples of participants during exacerbations when trying to quantify macrolide resistance rates. However, these pathogens may likely represent only a tip of the iceberg since the airway bacterial load in a patient on macrolide treatment will be suppressed and those patients are less likely to be able to produce sputum later on during the trial, due to a treatment effect. A more accurate way to establish the magnitude of resistance induction would be to quantify macrolide resistance in bacterial strains being carried as commensal bacteria by the individual and perhaps also in household contacts of individuals on long term macrolide treatment, since frequent transmission of commensal organisms among close contacts has been reported [36]. To determine the composition of both the respiratory and intestinal microbiota, study protocols should include nasopharyngeal swabs and collection of faeces specimen which –in view of the superior sensitivity of those techniques- should preferably be tested with molecular genetic tests e.g., fluorescence in situ hybridisation or 16S rRNA sequencing.

The antibacterial effects of azithromycin are likely to be independent of its anti-inflammatory activity. A very promising way to circumvent the problem of resistance induction is the development of novel, non-antibiotic macrolides, including the azithromycin derivate CSY0073 [37]. Although currently the evidence is limited to animal models, CSY0073 exhibits anti-inflammatory activity similar to regular azithromycin, without bacteriostatic activity [38].

Macrolide maintenance treatment has been shown to cause important reduction of respiratory symptoms and infectious exacerbations in patients with bronchiectasis [20-

22]. However, the lack of any concomitant improvement of structural airway damage in our simultaneously conducted radiological study, may suggest that the perceived clinical improvement is in fact no more than a very effective, but temporary suppression of inflammation. The structural damage to the airways itself does not appear to improve importantly [39]. In the last decade mechanisms involved in regeneration of lung tissue have been unveiled and this forms the basis of the rapidly advancing field of modern tissue engineering [40]. Great efforts are made to identify progenitor- or stem cells that have the ability to regenerate lost or damaged cells of airways or alveoli [41]. Translational research is needed to eventually repair structural lung injury, the major characteristic of bronchiectasis. Current treatment relies on symptoms relieve, reducing further structural damage to airways and lung tissue, while patients with critically advanced disease can only be salvaged by lung transplant.

Concluding remarks

Many things have changed since Dr Laennec first used his stethoscope to listen to the crackling breath sounds of a little boy suffering from bronchiectasis. Nowadays, a boy like the one Laennec examined would have a fair chance to survive into adulthood and, particularly if he happened to have severe symptoms, would probably be on azithromycin maintenance treatment right now, just as many of his fellow-patients.

Hopefully, they will grow older into a future where the individual risks and benefits of long term macrolide treatment will be known and prudential use of macrolides will be guided by either clinical traits, inflammatory markers or radiological disease severity. Only the ‘macrolide-responsive’ phenotype of bronchiectasis patients will be prescribed macrolides and other tailored treatment modalities will be available for other patient categories.

Ideally, the reduction of antibiotic use resulting from this approach will have caused a decrease in macrolide resistance rates and patients in whom macrolide treatment is justified will be periodically checked for the presence of unfavourable changes to their microbiota using modern sequencing techniques.

Ghandi himself once said “the future depends on what you do today” and this is particularly true for the rapidly changing field of *macrolide treatment for bronchiectasis.*

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